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Removal of Pharmaceuticals during Drinking Water Treatment

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The elimination of selected pharmaceuticals (bezafibrate, clofibric acid, carbamazepine, diclofenac) during drinking water treatment processes was investigated at lab and pilot scale and in real waterworks. No significant removal of pharmaceuticals was observed in batch experiments with sand under natural aerobic and anoxic conditions, thus indicating low sorption properties and high persistence with nonadapted microorganisms. These results were underscored by the presence of carbamazepine in bank-filtrated water with anaerobic conditions in a waterworks area. Flocculation using iron(III) chloride in lab-scale experiments (Jar test) and investigations in waterworks exhibited no significant elimination of the selected target pharmaceuticals. However, ozonation was in some cases very effective in eliminating these polar compounds. In lab-scale experiments, 0.5 mg/L ozone was shown to reduce the concentrations of diclofenac and carbamazepine by more than 90%, while bezafibrate was eliminated by 50% with a 1.5 mg/L ozone dose. Clofibric acid was stable even at 3 mg/L ozone. Under waterworks conditions, similar removal efficiencies were observed. In addition to ozonation, filtration with granular activated carbon (GAC) was very effective in removing pharmaceuticals. Except for clofibric acid, GAC in pilot-scale experiments and waterworks provided a major elimination of the pharmaceuticals under investigation.

Introduction

In Germany, some pharmaceuticals are used in quantities of more than 100 t/yr (*1*). Pharmacokinetic studies exhibit that an appreciable proportion of the administered pharmaceuticals are excreted via feces and urine (*2*) and thus are present in the domestic wastewater. A further source for the contamination of wastewater is assumed to be the disposal of (expired) medicine via toilets. However, this portion is very difficult to estimate because reliable data are not available. After passing through sewage treatment plants (STPs), pharmaceutical residues enter receiving waters. Point discharges from pharmaceutical manufacturers can also contribute to contamination of rivers and creeks (*3*). First results concerning environmental occurrence of pharmaceuticals are reported by Garrison et al. (*4*) and Hignite and Azarnoff (*5*), who detected clofibric acid in the lower micrograms per liter range in treated sewage in the United States. Further studies in 1981 in Great Britain revealed that pharmaceuticals are present in rivers up to 1 μg/L (*6*). On Iona Island (Vancouver, Canada) Rogers et al. (*7*) identified the two antiphlogistics ibuprofen and naproxen in wastewater. Recent investigations showed the exposure of a wide range of pharmaceuticals from many medicinal classes (e.g., betablockers, sympathomimetics, antiphlogistics, lipid regulators, antiepileptics, antibiotics, vasodilators) to rivers and creeks. Reviews from Halling-Sørensen et al. (*8*), Daughton and Ternes (*9*), and Jørgensen et al. (*10*) summarize most of the literature in this new emerging field about the environmental relevance of pharmaceuticals. Furthermore, Möhle et al. (*11*), Alder et al. (*12*), Ternes et al. (*3*), and Zuccato et al. (*13*) have reported the identification of pharmaceuticals in the aquatic environment.

Contamination is influenced by the relative portions of raw and treated wastewater (*14*) such that even small rivers and creeks can be highly contaminated. Groundwater is contaminated with pharmaceuticals primarily by infiltration of surface water containing pharmaceutical residues as well as by leaks in landfill sites and sewer drains. Because of the widespread occurrence of pharmaceuticals in the aquatic environment and sometimes also in the raw water of waterworks, a few cases surfaced where pharmaceuticals were detected in drinking water in the lower nanograms per liter range (*15*, *16*). Although up to now no adverse health effects can be attributed to the consumption of pharmaceuticals at these low concentration levels, based on precautionary principles, drinking water should be free of such anthropogenic contaminants.

Currently, few papers have been published dealing with the removal of pharmaceuticals in drinking water treatment. Ozonation and especially advanced oxidation processes seem to be very effective in removal of diclofenac, while clofibric acid and ibuprofen were oxidized in lab-scale experiments mainly by ozone/H_2O_2 as shown by Zwiener and Frimmel (*17*). Heberer et al. (*18*) exhibited that reverse osmosis is appropriate to remove a variety of different pharmaceuticals from highly contaminated surface waters.

The objective of the work presented here was to study the efficiency of different treatment steps to remove the antiphlogistic diclofenac, the antiepileptic carbamazepine, and the lipid regulators clofibric acid and bezafibrate during drinking water treatment. Therefore, the primary elimination of the selected pharmaceuticals was investigated under laboratory, pilot, and real waterworks conditions. In addition to processes such as bank filtration and artificial groundwater recharge, widely used techniques for surface water treatment such as activated carbon filtration, ozonation, and flocculation were investigated. The monitoring results of two German waterworks are extended by lab- and pilot-scale experiments to obtain more generalized results.

Experimental Section

Selected Pharmaceuticals. For all lab- and pilot-scale spiking experiments, four relevant pharmaceuticals (the antiphlogistic diclofenac, the antiepileptic carbamazepine, the lipid regulators clofibric acid and bezafibrate) have been selected

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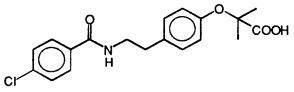
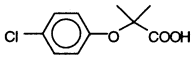
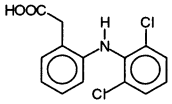
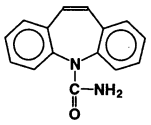
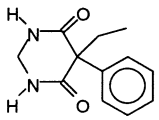
TABLE 1. Selected Target Pharmaceuticals

Name	CAS-number	Chemical structure	Application
Bezafibrate	41859-67-0		lipid regulator
Clofibric acid	882-09-7		metabolite of lipid regulators clofibrate, etofibrate, theofibrate
Diclofenac	15307-86-5		antiphlogistic
Carbamazepine	298-46-4		antiepileptic
Primidone	144-11-6		antiepileptic

as target compounds. Their molecular structures are shown in Table 1. These compounds have been chosen because of their predominant occurrence in German feeding waters for waterworks such as rivers, bank filtrates, and groundwater (*14*, *19*). Additionally, the antiepileptic primidone was included in oxidation experiments and a waterworks survey.

Analytical Methods. The determination of the pharmaceuticals was performed using different analytical methods (see Table 2). All methods were based on a solid-phase extraction of the analytes on to RP-C_{18} or Lichrolute EN material. After solid-phase extraction (SPE) and an elution step with methanol or acetone, the compounds were derivatized using different agents. Either a methylation with diazomethane (*20*) or a silylation with a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 5% trimethylchlorosilane (TMCS) (Fa. Fluka, Buchs, Schweiz) were used (60 min at 120 °C) (*21*). Carbamazepine was determined after silylation either by a mixture of MSTFA/TMSI/DTE (*N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide/trimethylsilylimidazol/dithioerytrit; 1000 μL/2 μL/2 μg) (*22*) or by a mixture of BSA/TMCS. For primidone, an acetylation by acetanhydride and ethanolamine was used (*22*). In all cases, GC−MS was used for the detection of the analytes. Further details of the methods are reported in refs *19*−*22*.

All methods enable the precise determination of the target pharmaceuticals in river water and drinking water. An interlaboratory comparison exercise (ICE) between the three participating laboratories at the beginning and the end of the study confirmed the quality of the analytical methods. Groundwater and surface water samples were spiked with the selected pharmaceuticals and analyzed by all three laboratories to confirm the recoveries of the analytes in the respective matrixes. The mean recovery of the spiked concentrations always exceeded 70% through different spiking levels: 0.40−0.90 μg/L in surface water and 0.030−0.20 μg/L in drinking water. The relative standard deviations between the three participating laboratories were in general below 25%. Thus, it could be shown that (i) the difference of found concentrations was minor between the three laboratories and (ii) the spiked concentration could be detected in the groundwater and surface water accurately.

Limits of Quantification (LOQ) and Calibration. The LOQ was calculated according to the German DIN 32645 (*23*) with a confidence interval of 99% using the standard deviation of a linear regression curve. Calibration ranges from 0.005 to 0.050 μg/L and from 0.05 to 1 μg/L were used with at least seven concentration levels by spiking groundwater. LOQ is another term for limit of determination (LOD) mentioned in DIN 32645. Since the calculated LOQ values were always between the first and the second calibration points, the LOQ used was set as the second lowest calibration point of the linear correlation to ensure a precise quantification. Hence, the LOQ were at least 20 ng/L for diclofenac, carbamazepine, primidone, and clofibric acid and down to 50 ng/L for bezafibrate. However, with a final volume of 100 μL instead of 1 mL, LOQ down to 2 ng/L were achieved for clofibric acid, primidone, diclofenac, and carbamazepine and down to 10 ng/L for bezafibrate. The calibration was performed over the whole procedure after spiking groundwater with the standard mixture of the selected pharmaceuticals. The calculation of the concentrations in native samples was carried out using surrogate standards (see Table 2) and a linear 7−10 point calibration curve.

Reference Standards. The reference standards clofibric acid, bezafibrate, carbamazepine, diclofenac, and primidone as well as the surrogate standards meclofenamic acid and 2,3-dichlorophenoxyacetic acid (2,3-D) were purchased from Sigma, Germany; dihydrocarbamazepine was purchased from Alltech, Germany. All standards were dissolved in methanol (1 mg/mL) and diluted with methanol to the final stock solution of 10 μg/mL.

Treatment Processes Used in Waterworks. (a) Study of Biodegradation in Batch Experiments with Native Surface Water, Groundwater, and Different Filter Materials. Biodegradation is one of the crucial factors that determine the elimination of organic compounds during artificial groundwater recharge and bank filtration. To assess the general biodegradability of pharmaceuticals in aquatic environmental matrixes, batch experiments were carried out according to

TABLE 2. Analytical Methods Used for Determination of the Target Pharmaceuticals

	method A acid compounds[a]	method B carbamazepine	method C acid compounds[a]/ carbamazepine	method D primidone
sample vol (L)	1	1	1	1
filtration	glass fibers (<1 μm)	glass fibers (<1 μm)	glass fibers (<1 μm)	glass fibers (<1 μm)
pH	2.0	7.5	3.0	7.5
SPE material	0.5 g of RP-C_{18} (Isolut)	1 g of RP-C_{18}ec (Baker)	1 g of RP-C18 (IST)	0.5 g of EN (Merck)
elution	3 mL of methanol, evaporation to dryness, addition of 1 mL of *n*-hexane	4 mL of methanol, evaporation to dryness	4 mL of acetone evaporation to dryness	4 mL of methanol, evaporation to dryness
derivatization	addition of diazomethane	50 μL of silylation mixture A[b] (for 60 min at 120 °C)	100 μL of silylation mixture B[c] (for 60 min at 120 °C)	160 μL acetic anhydride/ triethylamine (1:1)
surrogate standard	meclofenamic acid	dihydrocarbamazepine	2,3-dichlorophenoxyacetic acid (2,3-D)	dihydrocarbamazepine
GC/MS	HP 5890 GC HP 5970 MSD	HP 5890 GC HP 5971 MSD	GCQ (Finnigan MAT)	GC 8000, MD 800 (Fisons)
GC column	XTI-5 (30 m × 0.25 mm × 0.25 μm, Restek)	DB5 (30 m × 0.25 mm × 0.25 μm, J&W)	DB35 (30 m × 0.25 mm × 0.25 μm, J&W)	XTI-5 (30 m × 0.25 mm × 0.25 μm, Restek)
injection	2 μL split/splitless at 270 °C	5 μL cold injection (Gerstel, Germany)	2 μL split/splitless at 275 °C	3 μL split/splitless at 270 °C
temp program	50 °C (1.5 min) 20 °C/min to 120 °C 6 °C/min to 200 °C 9 °C/min to 290 °C (10 min)	50 °C (1 min) 20 °C/min to 170 °C 8 °C/min to 300 °C (6 min)	50 °C (2 min) 16 °C/min to 180 °C 5 °C/min to 300 °C (3 min)	50 °C (1 min) 20 °C/min to 160 °C 4 °C/min to 280 °C 20 °C/min to 300 °C (10 min)
scan mode	SIM	SIM	full scan (range m/z = 80−400)	SIM
literature	*20*	*22*	*21*	*22*

[a] Diclofenac and clofibric acid. [b] Mixture A: *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA)/trimethylsilylimidazol (TMSI)/dithioerytrite (DTE); 1000 μL/2 μL/2 μg (30 min at 80 °C). [c] Mixture B: 95% *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 5% trimethylchlorosilan (TMCS) (Fluka, Switzerland).

the OECD guidelines for testing chemicals (*24*). The inoculum used consisted of 400 mL of surface water and 400 mL of groundwater mixed with 2 L of MITI basal medium. The MITI basal medium was prepared by mixing 1 L of sterile deionized water with 3 mL of sterilized solutions A−D. Solution A was a solution of 21.75 g of K_2HPO_4, 8.5 g of KH_2PO_4, 44.6 g of $Na_2HPO_4 \cdot 12H_2O$, and 1.7 g of NH_4Cl in 1000 mL of deionized water at pH 7.2. Solutions B−D were solutions of 22.5 g of $MgSO_4 \cdot 7H_2O$, 27.5 g of $CaCl_2$, and 0.25 g of $FeCl_3$, respectively, in 1000 mL of deionized water. The groundwater was taken from a German water catchment area with artificial groundwater recharge using slow sand filtration and bank filtration. The individual concentrations of bezafibrate, carbamazepine, clofibric acid, diclofenac, and ibuprofen were in the batch experiments adjusted to 0.1 and 100 μg/L. The batch experiments were exposed to either individual or a mixture of the selected pharmaceuticals. In stock solutions with ethanol, the concentrations of the tested pharmaceuticals were 0.5 mg/mL or 0.5 μg/mL, respectively. After being diluted (480 μL of stock solution in 2.4 L of culture solution), the concentration of ethanol in batch cultures was 0.02% (v:v). The cultures were always incubated in the dark for 28 d at 14 °C (in situ temperature). For anoxic conditions, 25 mg/L nitrate was added as an alternative electron acceptor. The bottles used were gastight. For aerobic sorption experiments, 400 g of sand or 400 g of gravel taken from the underground of a groundwater catchment area was used as inoculum and mixed with 2 L of MITI basal medium (solid phase/liquid phase = 1:5). Sand that is also used for the slow sand filters of a waterworks consists of a mean grain size range of 0.2−0.6 mm. This filter material showed a moderate permeability with a K_f coefficient of 4.3×10^{-4} m/s. The gravel (natural aquifer sediment) was very heterogeneous with a predominant fraction of 2−10 mm grain size and a K_f coefficient of 2.9×10^{-3} m/s. Sterile controls (sterilization for 1 h) were prepared to differentiate between sorption and microbial degradation. The sand contains 3.2 mg/g iron and 0.056 mg/g manganese. Coatings with iron and manganese hydroxides were detected in the gravel but were not quantified.

Esterase activities were measured to control the physiological status of microbial communities during the incubation of batch cultures. The hydrolysis of fluorescein diacetate (FDA) by esterase enzymes was determined according to the procedure of Schnürer and Rosswall (*25*). A 20-μL volume of FDA solution (20 mg/10 mL acetone, stored at −18 °C) was mixed with 3 mL of sample and 0.5 mL of HEPES buffer (0.1 M *N*-2-hydroxyethylpiperazine-*N*′-2-ethansulfonic acid sodium salt in deionized water, adjusted to pH 7.5; Merck). After being incubated (sterile conditions, 90 min at 20 °C, darkness), the fluorescein formation was immediately measured with a Perkin-Elmer fluorescence spectrometer LC (excitation at 480 nm, emission at 505 nm).

(b) Flocculation. For flocculation experiments in lab-scale experiments, a noncontinual procedure, the so-called "Jar test", was performed. Spiking concentrations, stirring velocity, and reaction times were selected according to parameters of the two waterworks monitored in parallel. The lab device used consists of glass beakers (v = 2 L) with stator, a stirrer with standardized stirrer geometry, and defined submerged stirring depths. The stirring velocity was adjusted according to the mean velocity gradient (G value), which is proportional to the introduced energy and thus to the aggregation of colloids (*26*). Under stirring (rpm: 400 min^{-1}), 0.1 mL of iron(III) chloride solution (40%) was added to 1.8 L of raw water (spiked with 1 μg/L pharmaceuticals). After a stirring time of 1 min, pH 7.5 was attained by adding $Ca(OH)_2$ (1 mol/L). Then, the aggregation to microflocs was achieved by stirring slowly for 20 min under 30 min^{-1}. After sedimentation for 20 min, a sample was taken from under the water surface,

TABLE 3. Behavior of Selected Pharmaceuticals in Batch Experiments[a]

mean C/C_0 after 28 d	C_0 (μg/L)	bezafibrate (%)	clofibric acid (%)	diclofenac (%)	carbamazepine (%)
surface water (aerobic)	100	119 (±32)	103 (±10)	93 (±7)	109 (±16)
	0.1	113 (±7)	110 (±10)	94 (±6)	88 (±19)
groundwater (aerobic)	100	119 (±30)	105 (±9)	98 (±7)	104 (±3)
	0.1	100 (±13)	96 (±7)	104 (±6)	106 (±3)
groundwater (anoxic)	100	88 (±23)	91 (±9)	89 (±13)	105 (±24)
	0.1	87 (±27)	82 (±14)	106 (±14)	103 (±37)
sand plus groundwater	100	76 (±32)	96 (±10)	99 (±11)	91 (±26)
sand plus groundwater (sterile)	100	79 (±31)	97 (±23)	91 (±27)	65 (±35)
gravel plus groundwater	100	60 (±39)	85 (±19)	92 (±12)	120 (±27)
gravel plus groundwater (sterile)	100	85 (±20)	90 (±14)	106 (±19)	76 (±32)

[a] Mean relative concentration C/C_0 after 28 d and RSD in parentheses.

and the turbidity was measured. These measurements showed that the turbidity was always below 1.5 turbidity units of formazine (TU/F).

(c) Activated Carbon Adsorption. *Adsorption Isotherms.* For the determination of the adsorption isotherms, the following parameters have been used: (i) 200 mL of deionized water or groundwater spiked with initial concentrations of 100 μg/L of the pharmaceuticals under investigation, (ii) pulverized granular activated carbon based on coal, (iii) quantities of activated carbon varied to achieve a final concentration of the pharmaceuticals in the solution that is at least 2 orders of magnitudes smaller than the initial one, (iv) small portions of activated carbon (<0.2 g/L) added as suspension, (v) batches with activated carbon tumbled in 250-mL flasks for 24 h, (vi) finally all samples were filtered with 0.45-μm polycarbonate filter and analyzed according to the analytical method described before. Evaluation of the isotherms was performed in double logarithmic scale according to Freundlich (*27*, *28*). For a single compound, the Freundlich equation $q = Kc^n$ describes the relation between the loading q of the activated carbon and the equilibrium concentration c in the solution. K and n denote the Freundlich parameters.

Operation of a Granulated Activated Carbon (GAC) Adsorber in Pilot Scale. A pilot plexiglass filter was operated in down flow mode to investigate the removal of the selected pharmaceuticals by GAC filtration. The empty bed contact time was about 10 min with a flow velocity of 10 m/h. The filter was filled with fresh granular carbon based on coal, which is often used in drinking water facilities. The filter was operated with groundwater from a waterworks, which was before aerated and filtered to remove iron precipitations. The influent was spiked with bezafibrate, carbamazepine, diclofenac, and clofibric acid. The pilot filter was operated for nearly 9 months. In intervals of 14 d, the concentrations of the pharmaceuticals were analyzed in the filter influent, at five different heights and in the final filter effluent at a bed depth of about 160 cm. The mean influent concentrations of the pharmaceuticals were 1.8 μg/L for clofibric acid, 1.0 μg/L for carbamazepine, 0.26 μg/L for bezafibrate and 0.04 μg/L for diclofenac. The different spiked concentrations were due to the limited solubility of the target compounds in the feeding water.

(d) Ozonation. In a lab-scale device, water was ozonated in 2-L glass bottles by bubbling ozone through the samples in order to simulate real waterworks conditions. By varying the bubbling time, definite ozone doses in the range of 0.5−3.0 mg/L were introduced into the water. The water was continuously stirred at 900 rpm min^{-1}. After a reaction time of 20 min, the remaining ozone was quenched by adding sufficient sodium thiosulfate solution (c = 2.2 g/L) to the sample. To determine the transferred ozone doses as a function of the bubbling time, Milli-Q water was ozonated, and the dissolved ozone was measured (external calibration of the ozone doses) according to DIN 38408 using *N,N*-diethyl-*p*-phenylendiamine (DPD) purchased from Sigma, Germany (*29*). The transferred ozone doses through the system into Milli-Q water was further confirmed by the indigo method (*30*). Flocculated water of a waterworks was spiked with the selected pharmaceuticals (dissolved in 50 μL of methanol) prior to ozonation. Afterwards the ozone was bubbled through the spiked water sample for specific times corresponding to desired ozone doses. The half-life of ozone in the post-flocculated water was approximately 12 min.

Sampling Procedure. Water samples were collected in brown glass bottles that had been prewashed with successive rinses of Milli-Q water and acetone and were dried for 8 h at 250 °C. Samples were either extracted immediately or stored at 4 °C for a maximum period of 3 d.

Grab samples of the waterworks were taken before and after crucial treatment processes of two German waterworks with different treatment trains. All cooled water samples (4 °C) were analyzed as soon as possible (latest after 3 d).

(e) Treatment Trains of the Selected Waterworks. The following treatment processes were applied in the two waterworks selected in the current study.

Waterworks I (WW-I). Pre-ozonation (ozone dose: 0.7−1.0 mg/L; contact time: ca. 3 min), flocculation with iron(III) chloride, main ozonation (ozone dose: 1.0−1.5 mg/L; contact time: ca. 10 min), multiple layer filter, and a final GAC filtration.

Waterworks II (WW-II). Sedimentation, flocculation with $FeCl_3/CaOH_2$, GAC filtration, underground passage, bank filtration, and slow sand filtration.

Results and Discussion

Study of Biodegradation in Batch Experiments with Native Surface Water, Groundwater, and Filter Materials. Experiments with batch cultures could provide the first clues on the general potential for biodegradation of pharmaceuticals under different environmental conditions. The relative concentrations (C/C_0) of the spiked pharmaceuticals in the batch experiments with surface water and groundwater were nearly constant during the whole exposure time of 28 d (Table 3). All variations of elimination rates were within the relative standard deviation (RSD), which was between 6 and 39%.

Thus, it can be ruled out that significant sorption effects and biodegradation occurred in the waters and materials used under anoxic and aerobic conditions. These results suggest that the sorption properties of the selected pharmaceuticals can be expected to be low and that their persistence should be relatively high under real conditions such as slow sand filtration or subsoil passage. However, in complex habitats, the bioavailability and the sorption behavior are determined by various biotic and abiotic parameters that were not simulated in the described batch cultures. Parameters such as the species and physiological status of occurring microorganisms, the percentage of humic

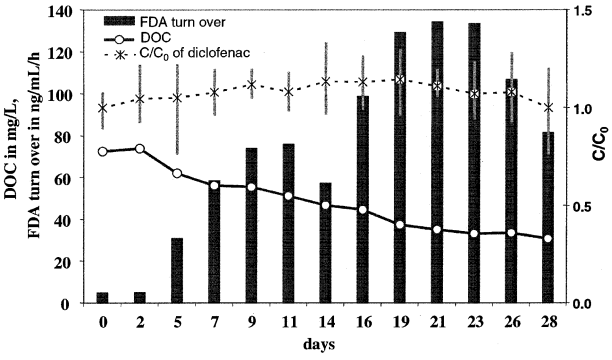


FIGURE 1. Esterase activity (hydrolysis of FDA), DOC degradation, and relative concentrations of diclofenac in a batch experiment with surface water spiked with 100 μg/L diclofenac (RSD of FDA turnover: 5−10%).

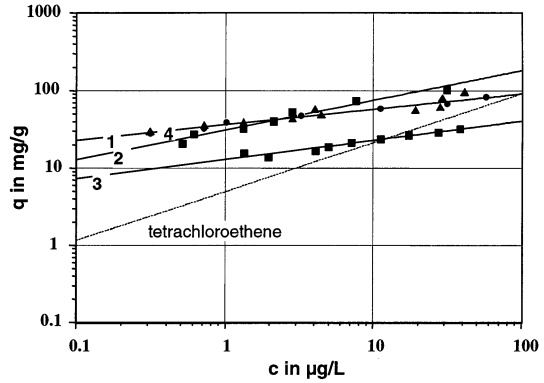


FIGURE 2. Adsorption isotherms of bezafibrate (1), carbamazepine (2), clofibric acid (3), diclofenac (4), and tetrachloroethene on fresh activated carbon Milli-Q water (isotherms of bezafibrate and diclofenac are identical within the accuracy of the applied method), spiked concentration: 100 μg/L.

TABLE 4. Freundlich Parameters of Pharmaceuticals after Adsorption from Deionized Water and Groundwater on Activated Carbon

	deionized water		groundwater	
	n	*K* (mg g^{-1} [(mg L^{-1})$^{-1}$]^{n})	*n*	*K* (mg g^{-1} [(mg L^{-1})$^{-1}$]^{n})
bezafibrate	0.19	141	0.22	77
carbamazepine	0.38	430	0.22	90
clofibric acid	0.25	71	0.54	63
diclofenac	0.19	141	0.21	36

substances, percentage of iron and manganese hydroxides, pH, etc. can differ significantly according to the actual field conditions. The standardized test used according to the OECD guidelines (*24*), delivers comparable results for the biodegradability of substances but cannot be transferred to all natural conditions and account for the various parameters. Therefore, on the basis of the described results, (bio)-degradation or sorption of the selected pharmaceuticals under field conditions cannot be ruled out in general, but they should be relatively low. Sorption of the selected pharmaceuticals on iron hydroxides seems to be insignificant since in the flocculation experiments with precipitated iron hydroxides no reduction of the spiked concentrations was found (see flocculation section below). Furthermore, it was observed that the established microbial activity in the test system was high enough for degradation of dissolved organic matter (DOC) and could not be inhibited by the spiked

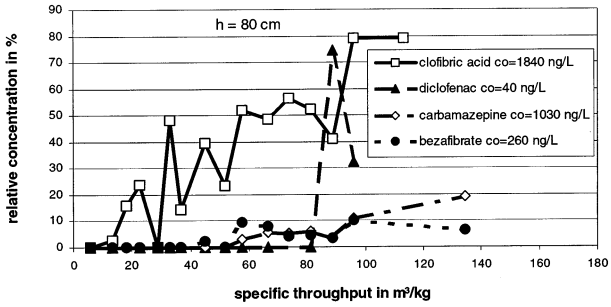


FIGURE 3. Relative concentrations of the breakthrough of the pharmaceuticals under investigation at a filter height of 80 cm of GAC filters filled with fresh activated carbon.

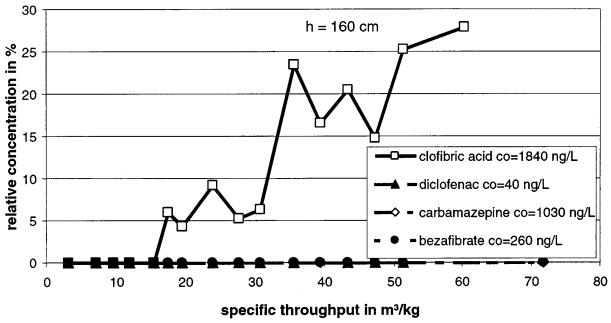


FIGURE 4. Relative concentrations of the breakthrough of the pharmaceuticals under investigation at a filter height of 160 cm of GAC filters filled with fresh activated carbon.

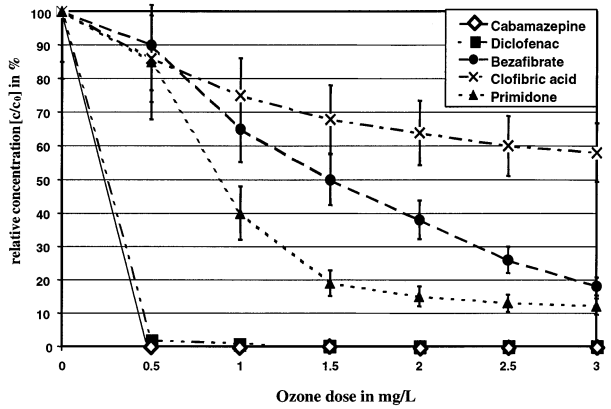


FIGURE 5. Removal of target pharmaceuticals using various ozone concentrations with flocculated water of WW-II in lab-scale experiment. Spiked concentrations: each 1 μg/L.

pharmaceuticals as it can be seen by the esterase activity (Figure 1).

Removal after Flocculation with Iron(III) Chloride. Flocculation in lab-scale (Jar test) with iron(III) chloride exhibited no significant elimination of the pharmaceuticals from raw water. The relative concentration levels (C/C_0) after flocculation were 96 ± 11% for diclofenac, 87 ± 10% for clofibric acid, 111 ± 15% for bezafibrate, 87 ± 12% for carbamazepine, and 110 ± 14% for primidone. Thus, c/c_0 of the spiked compounds varied without exception within the RSD. The transference of these results from lab-scale to waterworks conditions was shown by a monitoring of up-scaled flocculation processes in two waterworks (WW-I, WW-II; see section below: behavior in waterworks) yielding similar results.

Activated Carbon Adsorption. *Adsorption Isotherms.* The assessment of the adsorption properties of single compounds onto activated carbon is often performed by recording

TABLE 5. Parameters of WW-I That Were Also Used for Simulation in Lab-Scale and of WW-II at the Sampling Dates

	WW-I	WW-II	WW-II	WW-II	WW-II
sampling date	15.03.99	01.07.98	07.07.98	09.07.98	07.12.98
raw water temp (°C)	9.9	25.0	23.9	22.6	7.1
DOC (mg/L)	2.4	2.1	2.2	2.3	2.3
pH value raw water	8.0	7.9	8.0	8.0	8.0
pH value after flocculation	7.1	7.8	8.0	7.7	7.7
pre-ozonation: ozone dose (mg/L)	1.0				
pre-ozonation: reaction time (min)	3.0				
addition of Fe^{3+} (mg/L)	5.55−5.75	12.6	12.4	12.6	10.4
main ozonation: ozone dose (mg/L)	1.2				
main ozonation: reaction time (min)	10				
average GAC load (m^3/kg)		27.8	29.3	29.3	39.9

adsorption isotherms. Freundlich adsorption isotherms with fresh activated carbon were performed for each of the four selected pharmaceuticals. The isotherms are given in Figure 2. Bezafibrate, carbamazepine, and diclofenac exhibited over the whole concentration range (0.1−100 μg/L) a higher activated carbon loading q than did clofibric acid. Hence, clofibric acid has the lowest sorption affinity on activated carbon. In addition to the selected pharmaceuticals, the isotherm of tetrachloroethene is shown in Figure 2. Tetrachloroethene was used because its removal by adsorption onto activated carbon in full-scale treatment plants is known to be efficient (*31*). In a concentration range below 10 μg/L, the isotherms of the pharmaceuticals selected exhibited higher loads on carbon as compared to tetrachloroethene. Thus, it can be concluded that the four selected pharmaceuticals can be removed efficiently under real conditions by activated carbon filtration in waterworks.

Nevertheless, sorption efficiencies are always relying on the competition with other occurring organic compounds. As expected, the adsorption capacity for the pharmaceuticals is lower on activated carbon if other compounds such as natural organic substances compete for the adsorption sites. That can be underscored by a comparison of the Freundlich parameters for the adsorption with deionized water and with natural groundwater (DOC = 2.0 mg/L; SAC at 254 nm = 5.8 m^{-1}) given in Table 4. The shift toward lower K values is equivalent to a lower sorption capacity. Especially for clofibric acid the slope of the isotherm (n value) is relatively high in groundwater, which can be interpreted as a low adsorption capacity in the low concentration range. On the basis of the isotherms with natural groundwater, it can be expected that the capacity reduction of activated carbon might be significant due to competitive adsorption of natural groundwater constituents. Hence, the adsorption capacity of the activated carbon in a fixed bed adsorber in waterworks is expected to be lower for pharmaceuticals than in the isotherm experiments performed with deionized water.

GAC Filtration in Pilot Scale. In pilot-scale experiments, an activated carbon adsorber filled with activated carbon was operated according to the previous description. The breakthrough curves in different filter bed depths of about 80 cm and 160 cm (end of filter) are shown in Figures 3 and 4. These results coincide very well with the data of the isotherm tests listed in Table 4. Carbamazepine showed the highest adsorption capacity of the selected pharmaceuticals and can be removed at a specific throughput of about 50 m^3/kg in a carbon layer of 80 cm and more than 70 m^3/kg in a layer of 160 cm even at a relatively high initial concentration of about 1 μg/L. Clofibric acid, with an initial concentration of about 1,8 μg/L, showed a significantly lower adsorption capacity in the isotherm test and in the pilot-scale experiment. An initial breakthrough of clofibric acid could be observed at a height of 80 and 160 cm at a specific throughput of 10 and 17 m^3/kg, respectively. Although lower adsorption capacities in the isotherm test are observed for bezafibrate and diclofenac as compared to carbamazepine, both compounds were removed in a bed depth of 160 cm to a specific throughput of at least 70 m^3/kg. The differences between the results obtained in isotherm and the pilot plant experiments might be influenced by the lower initial concentrations applied in the pilot plant experiments

TABLE 6. Pharmaceutical Removal in Lab Scale (Simulation of WW-I Conditions) and in WW-I

	simulation in lab scale[a]		waterworks WW-I[a]	
	after preozonation	after main ozonation	after preozonation	after main ozonation
carbamazepine	>99	>99	96 ± 3	>99
clofibric acid	36 ± 15	57 ± 17	18 ± 13	77 ± 5
diclofenac	>99	>99	92 ± 8	>99

[a] Relative removal in %.

Ozonation. For lab-scale ozonation experiments, flocculated WW-II water was used. The DOC of the flocculated water was 1.3 mg/L, the pH was 7.8, alkalinity was 2 mmol/L, and temperature was 23 °C. The initial concentration of the pharmaceuticals under investigation was 1 μg/L. The efficiency of the ozonation process for the removal of the pharmaceuticals turned out to be very product specific. At a small ozone dose of 0.5 mg/L, the concentrations of diclofenac and carbamazepine were reduced by more than 97% while clofibric acid decreased by only 10−15% for the same ozone dose (Figure 5). Even extremely high ozone doses up to 2.5−3.0 mg/L led to a reduction of ≤40% for clofibric acid. Primidone and bezafibrate were reduced by 50% at ozone concentrations of about 1.0 and 1.5 mg/L, respectively. While applying 3.0 mg/L ozone, still 10% of primidone and 20% of bezafibrate remained. Because of the presence of methanol (used for dissolving the spiked pharmaceuticals), ozone was partly transformed into OH radicals. Thus, the direct ozone reaction was probably underestimated, and the oxidation efficiency under waterworks conditions should be even slightly higher than found in lab scale. Although we did no additional work to elucidate the reactivity of the selected pharmaceuticals with ozone or OH radicals, we can rationalize these observations based on the chemical structures (Table 1). The reactivity of diclofenac and carbamazepine with ozone is expected to be very high. Rate constants $k_{O_3} > 10^5$ M^{-1} s^{-1} can be expected for deprotonated secondary aromatic amines (diclofenac) and molecules containing nonaromatic double bonds (carbamazepine) (*32*, *33*). For diclofenac, a main oxidation product was detected with a mass spectrum showing an increase of the molecular weight of 16 amu, which is an evidence for substitution of a hydrogen by a hydroxy moiety. A hydroxylation of the secondary amino group is likely but has to be confirmed (e.g., by NMR). Because of missing active sites susceptible to ozone attack (*34*), reactions of ozone with clofibric acid are expected to be very

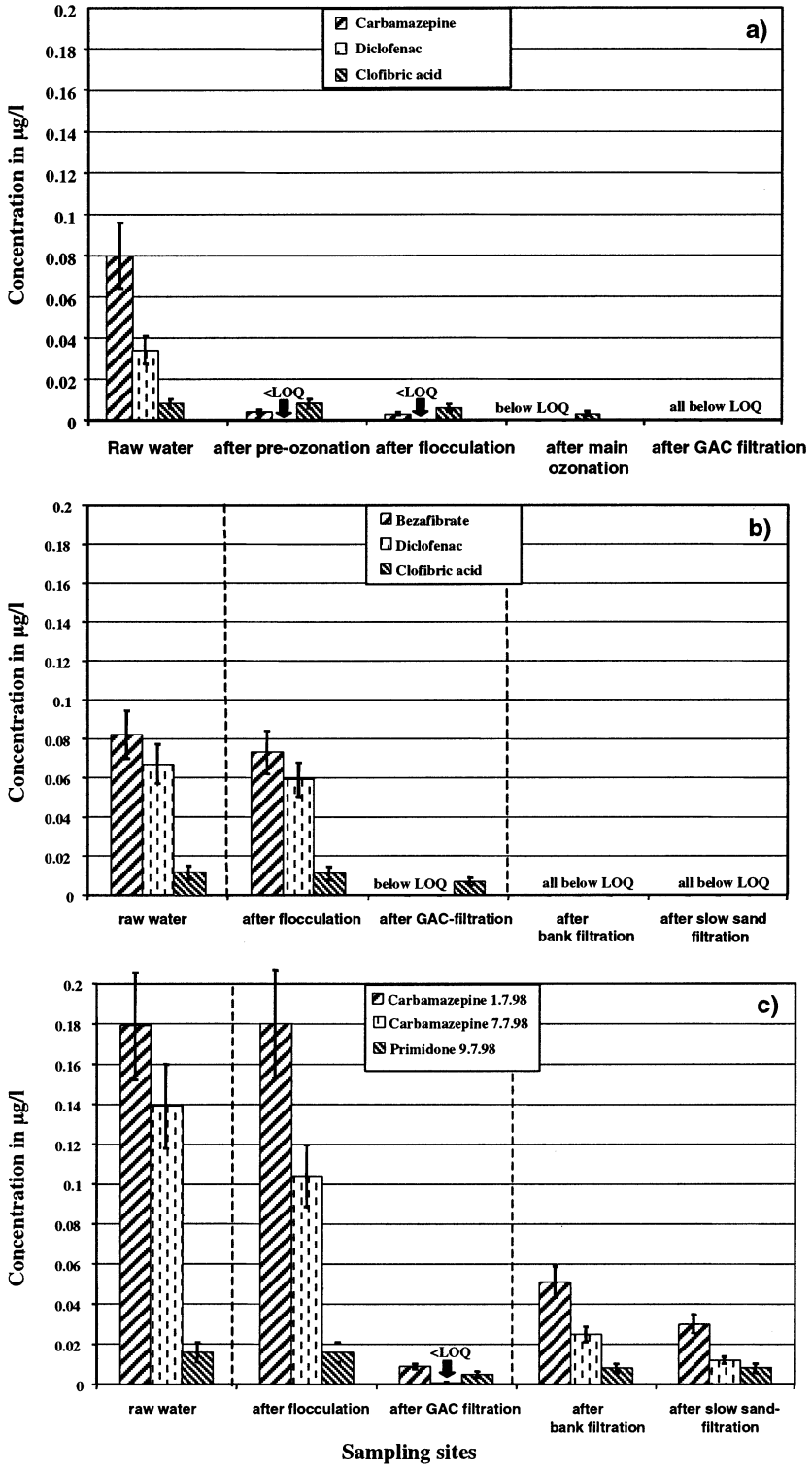


FIGURE 6. Concentrations of pharmaceuticals (a) in WW-I, March 15, 1999, and (b) in WW-II, December 7, 1998, and (c) in WW-II, July 1998.

slow. Thus, OH radical reactions should be predominant with $k_{OH} \sim 5 \times 10^9$ M^{-1} s^{-1} (*35*). Considering the OH radical activity taken from the prediction for clofibric acid, ozone rate constants for bezafibrate and primidone should result in the middle range ($k_{O_3} \sim 10^2 - 10^3$ M^{-1} s^{-1}). The reactivity of these pharmaceuticals with ozone can be based on their reactive mono- and disubstituted benzene rings (*32*). It has to be noted that in the current study only the primary target degradation was investigated, thus further research is essential to identify and confirm the structures of metabolites formed by ozonation and to clarify the kinetic behavior.

In parallel to a WW-I monitoring for pharmaceuticals (see below), a simulation in lab scale was performed using the feeding water of WW-I. Very similar flocculation conditions, ozone doses, pH values, contact times, and temperatures were applied in the lab-scale experiments (Table 5). Diclofenac and carbamazepine were totally removed under waterworks conditions and in the lab-scale experiments,

while only a minor part of clofibric acid was oxidized in the ozonation process (Table 6). However, it has to be noted that the concentration of clofibric acid was very low in the range of 2−10 ng/L. In general, the removal efficiency attained in lab-scale experiments were comparable to the waterworks conditions within the statistical error. Such experiments can therefore be used to assess oxidation of pharmaceuticals in full-scale ozonation systems. This has been demonstrated before by von Gunten et al. (*36*) and Kaiser et al. (*37*) for a variety of micropollutants.

Behavior in Waterworks. Water samples taken after preozonation, flocculation, and main ozonation of WW-I were analyzed for the target pharmaceuticals. Carbamazepine and diclofenac were detected in the feeding water of WW-I with 0.08 and 0.035 μg/L, respectively. Clofibric acid was detected in concentrations as low as 0.009 μg/L (Figure 6). Preozonation with 0.7 mg/L ozone reduced the concentrations of carbamazepine and diclofenac by more than 90%. Thus, remaining concentrations were below 0.010 μg/L. Flocculation with iron(III) chloride did not lead to a significant reduction of the pharmaceuticals. After main ozonation only clofibric acid was detected, and after passing GAC filter none of the target pharmaceuticals were found above the LOQ down to 2 ng/L.

In the raw water of WW-II (Table 5), clofibric acid, diclofenac, and carbamazepine were detected in the same concentration range as in WW-I, whereas bezafibrate and primidone were present with ca. 0.080 and 0.015 μg/L, respectively (Figure 6). Similar to the lab-scale results, the flocculation with iron(III) chloride proved ineffective in removing the selected pharmaceuticals. After GAC filtration, diclofenac and bezafibrate were not detected above LOQ, the concentrations of carbamazepine and primidone were reduced by more than 75%, and the concentration of clofibric acid was reduced by ca. 20% (Figure 6). A separate bank filtration of the raw water in WW-II showed the antiepileptics carbamazepine and primidone passing through soil under anaerobic conditions into the groundwater. Diclofenac and clofibric acid were however not found in the bank-filtrated water. Obviously, under real field conditions diclofenac can be removed during the anaerobic bank filtration. These finding were confirmed by data from other waterworks (*38*). Whether diclofenac exhibits special sorption properties or is alternatively biodegraded during anaerobic subsoil-passage were not elucidated. Further research is necessary to clarify these aspects. Removal of clofibric acid could not be confirmed due to its low concentrations caused in part by dilution from noncontaminated recharged groundwater occurring in that catchment area. Other studies reported a high stability for clofibric acid under various groundwater conditions (*39*). Whether the subsequent slow sand filtration in WW-II significantly removed the two antiepileptics is not conclusive since their reduction of 30% was close to the analytical standard deviation of ca. 20%.

Evaluation of the Treatment Processes. The behavior of the pharmaceuticals bezafibrate, carbamazepine, clofibric acid, and diclofenac in waterworks could be roughly confirmed by lab- and pilot-scale experiments. Slow sand filtration and flocculation by iron(III) chloride were very inefficient in removing trace levels of the selected pharmaceuticals. Obviously, their relative high polarity and missing sites for specific interaction in soil lead to nonappreciable sorption quantities. Since the stability of the pharmaceuticals under real conditions (anaerobic to aerobic) tends to be relatively high, they contaminate groundwater sometimes with enhanced concentration levels (*16*, *39*). Although diclofenac seems to be removable by bank filtration, the mechanism (sorption or biodegradation) is not yet known. GAC filtration was a very effective removal process. Even in relatively high concentrations, the pharmaceuticals could be almost completely removed at specific throughputs over 70 m^3/kg with the exception of clofibric acid. Clofibric acid is less prone to adsorption but could be removed completely at a specific throughput of 15−20 m^3/kg. Ozonation was very effective in oxidizing carbamazepine and diclofenac. It appreciably reduced the concentration levels of bezafibrate and primidone but only exhibited limited efficiency in removing clofibric acid. Thus, it is relatively unlikely that in waterworks, which use only flocculation and sand filtration, a substantially removal of most of the pharmaceutical residues takes place. An alternative to ozonation and GAC filtration can be seen in the use of nanofiltration and reverse osmosis (*40*), neither of which were tested in the current study.

If the raw water of waterworks is contaminated by polar pharmaceuticals, removal can only be assured using more advanced techniques such as ozonation, AOP, activated carbon, or membrane filtration. The contamination of the raw water is influenced mainly by its percentage of treated wastewater. In Germany, waterworks using surface water or bank filtrates of rivers are equipped with GAC, ozonation, or even both. Thus, a contamination of the drinking water by the investigated pharmaceuticals is rather unlikely considering the results of the current paper. Although these substances are currently not regulated in drinking water directives worldwide, precautionary principles should be employed so that the removal of pharmaceuticals be as high as possible through improved or existing treatment techniques. More care has to be taken when contaminated groundwater is used as the raw water for drinking water production. Waterworks using such feeding waters are in general not equipped with as advanced treatment techniques as those for waterworks treating surface waters.

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